Chemotherapy Protocol

COLORECTAL CANCER

CAPECITABINE-CETUXIMAB-OXALIPLATIN (21 day)

This regimen may require funding

Regimen

- Colorectal Cancer – Capecitabine-Cetuximab-Oxaliplatin (21 day)

Indication

- Cetuximab in combination with fluoropyrimidine and oxaliplatin chemotherapy is recommended as a possible first or second line treatment for people with metastatic colorectal cancer when:

  - surgery to remove the cancer in the colon or rectum has been carried out or is possible
  - the metastases are only in the liver and cannot be removed surgically before treatment
  - the person is fit enough to have surgery to remove the cancer in the colon or rectum and to have liver surgery if it becomes possible to remove the metastases after cetuximab treatment

- The tumour is positive for the wild type KRAS genotype

- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Capecitabine	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Cetuximab	Infusion related reactions, interstitial lung disease, skin reactions, electrolyte abnormalities, fatigue, abdominal pain, constipation
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- Prior to starting therapy confirm a positive KRAS status
- FBC, LFT's and U&E's prior to day one of treatment
- Monitor for hypersensitivity reactions for 60 minutes after the end of the cetuximab infusion
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with capecitabine. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing the following criteria must be met.

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

For haematological toxicity, if the neutrophil count is less than 1.5×10^9/L or the platelet count is less than 75×10^9/L, delay treatment until these levels are achieved. Re-initiate therapy at the full dose for a seven day delay or with 75% of the original dose for a fourteen day delay (consider re-starting with 100%). If the delay is more than 20 days stop therapy.

There is little need to adjust the dose of cetuximab for haematological toxicity.

Hepatic / Renal Impairment

Deteriorating liver or kidney function may be a sign of disease progression or drug toxicity.

Hepatic Impairment

Drug	Dose (% of original dose)
Capecitabine	There is little published information available. No dose reductions are necessary for those with mild to moderate hepatic dysfunction due to liver metastasis
Cetuximab	Administer only when the transaminases are 5xULN or below and the bilirubin is 1.5xULN or below
Oxaliplatin	There is little published information available. No dose reductions are probably necessary.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Capecitabine	More than 51	100
	30-50	75
	less than 30	Do not use
Cetuximab	more than 180 (1.5xULN)	Do not use
Oxaliplatin	Less than 20	Dose reduce and adjust according to toxicity

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes. Dose limiting toxicities include diarrhoea, abdominal pain, emesis, stomatitis, palmar-plantar erythrodysesthesia and neurosensory toxicities among others.

If any NCI-CTC grade 1 toxicity occurs treatment should be continued, without interruption, at the full dose.

For toxicities NCI-CTC grade 3 or above in general treatment should be withheld until recovery to at least NCI-CTC grade 1 then re-started if medically appropriate. If recovery takes twenty-one days or longer then stop treatment.

Capecitabine

NCI-CTC Grade 2

Interrupt treatment until the toxicity resolves to NCI-CTC grade 0-1 then continue at the same dose. If the toxicity recurs for a second time again interrupt treatment until it resolves to NCI-CTC grade 0-1 then resume therapy at 75% of the original dose. If the same adverse effect develops on a third occasion once more interrupt treatment until it resolves to NCI-CTC grade 0-1 then continue at 50% of the original dose. Stop treatment if the toxicity re-appears on a fourth instance.

NCI-CTC Grade 3

Interrupt treatment until the toxicity resolves to NCI-CTC grade 0-1 then continue treatment using 75% of the original dose with prophylaxis if appropriate. If the toxicity recurs for a second time again interrupt treatment until it resolves to NCI-CTC grade 0-1 and then resume therapy at 50% of the original dose. If the same adverse effect develops on a third occasion discontinue capecitabine.

NCI-CTC Grade 4

Discontinue treatment unless the responsible consultant considers it to be in the best interest of the patient to continue at 50% of the original dose once the toxicity has resolved to NCI-CTC grade 0-1.

When capecitabine is stopped for toxicity the doses are omitted, not delayed.

Consider stopping capecitabine therapy if chest pain occurs.

Cetuximab

Allergic or hypersensitivity reactions have occurred during the administration of cetuximab. For a NCI-CTC grade 1 reaction reduce the infusion rate by 50%. For a NCI-CTC grade 2 reaction, stop the infusion and administer supportive therapies as indicated. Once the reaction has resolved to NCI-CTC grade 1 or below resume the infusion at 50% of the previous rate. For a NCI-CTC grade 3 or 4 toxicity stop the infusion immediately and disconnect the tubing from the patient. Administer appropriate supportive therapies. Once recovered, patients should not receive cetuximab again.
Once the rate has been reduced it should not be increased on subsequent infusions.

If a second reaction occurs on the slower infusion rate the infusion should be stopped and no further treatment given.

An acniform skin rash occurs in over 70% of those receiving cetuximab. The onset is normally within three weeks of starting therapy and often resolves after week twelve. For a NCI-CTC grade 1-2 reaction use symptomatic treatments such as topical or oral antibiotics and continue with the cetuximab. For a NCI-CTC grade 3 toxicity delay treatment until the toxicity resolves to NCI-CTC grade 2 or below. If this occurs within fourteen days resume cetuximab at the same dose. If more than fourteen days is required stop treatment. If the NCI-CTC grade 3 toxicity occurs for a second and third time the cetuximab may again be delayed for up to and including fourteen days with concomitant dose reductions to 200mg/m^2 and 150mg/m^2 respectively. Cetuximab dose reductions are permanent. The cetuximab must be discontinued if more than two consecutive infusions are withheld or a fourth episode of a NCI-CTC grade 3 skin toxicity develops or a NCI-CTC grade 4 toxicity at any time.

UV radiation may worsen skin reactions. Sun safety practices should be followed during and for up to two months after the end of treatment.

Stop treatment if there is a confirmed pneumonitis.

Oxaliplatin

For cold related dysaesthesia or paresthesia without pain there is no need to dose delay or reduce unless it persists between cycles. In this instance withhold the oxaliplatin until recovery and then re-start treatment using 100mg/m^2. Only omit the oxaliplatin if it recurs.

For paresthesia with pain or functional impairment that lasts up to seven days no dose modification is necessary. If it persists beyond seven days or is NCI-CTC grade 3 and above, in the first instance reduce the dose to 100mg/m^2. If the painful paresthesia recurs or persists between cycles omit the oxaliplatin.
If NCI-CTC grade 3-4 diarrhoea or stomatitis recurs despite appropriate reduction in the capecitabine dose the oxaliplatin dose should be reduced to 100mg/m^2.

There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptom occurs stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

Regimen

21 day cycle for 6 cycles

Cycle One

Drug	Dose	Days	Route
Capecitabine	800mg/m^2 twice a day	1-14 incl	Oral
Cetuximab	400mg/m^2	1	Intravenous infusion (see administration)
Cetuximab	250mg/m^2	8, 15	Intravenous infusion (see administration)
Oxaliplatin	130mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

Cycle Two Onwards

Drug	Dose	Days	Route
Capecitabine	800mg/m^2 twice a day	1-14 incl	Oral
Cetuximab	250mg/m^2	1, 8, 15	Intravenous infusion (see administration)
Oxaliplatin	130mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

Dose Information

- Capecitabine will be dose banded in accordance with the national dose bands
- Cetuximab will be dose banded in accordance with the national dose bands (5mg/ml)

- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Cetuximab - neutral
- Oxaliplatin – exfoliant

Other

- Capecitabine should start on the evening of day 1
- Capecitabine should be taken with or after food
- Individuals should be monitored for hypersensitivity reactions for sixty minutes after finishing the cetuximab infusion. Do not administer other chemotherapy during this period.
- The rate of administration of cetuximab must not exceed 5mg/min for the first infusion (minimum 120 minutes). If well tolerated subsequent infusions may be given at a rate of 10mg/min (minimum 60 minutes).
- Oxaliplatin must never come into contact with sodium chloride 0.9%. Ensure the line is flushed with glucose 5% before and after each oxaliplatin infusion

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on **day one** only;

  - dexamethasone 8mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication;

  - dexamethasone 4mg twice a day oral for 3 days
  - metoclopramide 10mg three times a day when required oral

- 30 minutes prior to cetuximab infusion;

  - chlorphenamine 10mg intravenous
  - dexamethasone 8mg oral or intravenous (given as part of antiemetic regimen on day 1)
  - H_2 antagonist according to local formulary choice and availability
  - paracetamol 1000mg oral

- Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.

- Ensure the total daily dose of capecitabine is divided into two doses given twelve hours apart (the first should be administered in the evening of day one of the cycle) Serious toxicity has occurred where the total daily dose has been given twice a day.

- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.

References

1. Moosnann N, von Weikersthal LF, Vehling-Kaiser U et al. Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first line treatment for patients with metastatic colorectal cancer. AIO KRK-0104 – a randomised trial of the German AIO CRC study group. JCO 2011; 29 (8): 1050-1058.
2. Maughan TS, Adams RS, Smith CG et al. Addition of cetuximab to oxaliplatin based first line combination chemotherapy for the treatment of advanced colorectal cancer; results of the randomised phase III MRC COIN trial. Lancet 2011; 377 (9783); 2103-2114.

REGIMEN SUMMARY

Capecitabine-Cetuximab-Oxaliplatin (21 day)

Day One Cycle One

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous

3. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H_2 antagonist according to local formulary choice and availability
Administration Instructions:
Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;
- Ranitidine 50mg intravenous once only
- Famotidine 20mg oral once only
- Nizatidine 150mg oral once only
- Ranitidine 150mg oral once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

5. Cetuximab 400mg/m^2 intravenous infusion

An interval of 60 minutes should be left between administration of cetuximab and oxaliplatin

6. Ondansetron 8mg oral or intravenous

7. Oxaliplatin 130mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes

Take Home Medicines

8. Capecitabine 800mg/m^2 twice a day for 14 days oral

9. Dexamethasone 4mg twice a day for 3 days oral starting the day after oxaliplatin

10. Metoclopramide 10mg three times a day when required oral

Day Eight and Fifteen Cycle One

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous

3. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H_2 antagonist according to local formulary choice and availability

Administration Instructions:

Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;

- Ranitidine 50mg intravenous once only
- Famotidine 20mg oral once only
- Nizatidine 150mg oral once only
- Ranitidine 150mg oral once only

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5. Cetuximab 250mg/m^2 intravenous infusion

Day One Cycle Two Onwards

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous

3. Paracetamol 1000mg oral

Administration Instructions

Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H_2 antagonist according to local formulary choice and availability

Administration Instructions:

Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;

- Ranitidine 50mg intravenous once only
- Famotidine 20mg oral once only
- Nizatidine 150mg oral once only
- Ranitidine 150mg oral once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

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5. Cetuximab 250mg/m^2 intravenous infusion

6. Ondansetron 8mg oral or intravenous

7. Oxaliplatin 130mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes

Take Home Medicines

8. Capecitabine 800mg/m^2 twice a day for 14 days oral

9. Dexamethasone 4mg twice a day for 3 days oral starting the day after oxaliplatin

10. Metoclopramide 10mg three times a day when required oral

Day Eight and Fifteen Cycle Two Onwards

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous

3. Paracetamol 1000mg oral

Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H_2 antagonist according to local formulary choice and availability

Administration Instructions:

Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;

- Ranitidine 50mg intravenous once only
- Famotidine 20mg oral once only
- Nizatidine 150mg oral once only
- Ranitidine 150mg oral once only

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5. Cetuximab 250mg/m^2 intravenous infusion

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.3	October 2020	Update of premedication due to shortage of IV ranitidine. IV ranitidine changed to H_2 antagonist according to local formulary choice and availability Coding removed Monitoring updated with DPD testing	Arum Shortland Pharmacist	Dr Debbie Wright Pharmacist
1.2	May 2014	Header changed Metoclopramide dose changed to 10mg Cetuximab administration changed to reflect SPC Mucositis recommendation changed Bolus removed from supportive therapies Coding updated Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Nov 2011	In the "Additional Therapy" section, dexamethasone added to the cetuximab premedication with statement regarding anti-emetic on day 1. Ondansetron moved in the regimen summary to be given after the cetuximab. In the regimen summary spelling of chlorpheniramine changed to chlorphenamine Spelling mistakes in dose modifications corrected (with out to without and paresthesiae to paresthesia)	Dr Debbie Wright Pharmacist	Becky Wills Pharmacist
1	Sept 2011	None	Dr Debbie Wright Pharmacist	Dr Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust

University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.